Plasmodium ovale Infection After One Year Mefloquine Prophylaxis in A Young Indonesian Soldier: A Case Report

Frans Liwang[1], Dewi M. Ratih[1], Soroy Lardo[2]

[1] Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia.

[2] Department of Internal Medicine, The Central Army Gatot Soebroto Hospital, Jakarta, Indonesia.

Corresponding Author:

Frans Liwang, MD. Department of Internal Medicine, Faculty of Medicine Universitas Indonesia – Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Jl. Diponegoro no. 71, Jakarta 10430, Indonesia. email: fr_archy02@yahoo.com.

ABSTRAK

Kemoprofilaksis malaria menggunakan meflokuin telah menjadi regimen standar WHO bagi anggota militer yang berada di daerah endemik dalam jangka waktu cukup panjang. Dalam laporan kasus ini disajikan kasus infeksi Plasmodium ovale pada anggota muda militer Indonesia yang telah mendapat profilaksis meflokuin 250 mg/minggu selama satu tahun. Pasien tersebut mengalami demam mengigil yang tipikal setelah kembali dua minggu dari tugas di Kongo, Afrika Barat-Tengah. Diagnosis malaria ovale ditegakkan melalui pulasan darah tepi, dan ditemukan 35/250 parasit dalam lapang pandang kecil mikroskop. Kasus kegagalan profilaksis jangka panjang pada dasarnya jarang ditemui, mengingat meflokuin telah menjadi obat pencegahan malaria, bahkan untuk kasus Plasmodium multi-resisten. Diduga, stadium dorman dari Plasmodium ovale, resistensi golongan obat kuinolin, dan efikasi meflokuin menjadi penyebab terjadinya fenomena tersebut.

Kata kunci: *plasmodium ovale, meflokuin, profilaksis malaria, malaria tertiana.*

ABSTRACT

Malaria chemoprevention using mefloquine has become the WHO standard regimen for military personnel who stay in the endemic area for an extended period of time. We reported a case of Plasmodium ovale infection in a young Indonesian Soldier following one year mefloquine prophylaxis 250 mg weekly. Typical fever and chills were experienced two weeks after returning from one year duty in Congo, West-Central Africa. The diagnosis of ovale malaria was made by peripheral blood smear, and 35/250 parasites in small microscopic view was found. Then, he recovered after dihydroartemisin and primaquine combination therapy. This was an unusual case of long-term prophylaxis failure since mefloquine has been recognized as the agent for malaria prevention, even multi-drug-resistance Plasmodium. Dormant stage of Plasmodium ovale, quinoline-resistance potential, and the efficacy of mefloquine itself are discussed as the cause of that phenomenon.

Keywords: *plasmodium ovale, mefloquine, malaria prophylaxis, tertiana malaria.*

INTRODUCTION

Chemoprophylaxis is one of the main approaches to prevent malaria worldwide.[1] It aims to prevent the occurrence of the symptoms of malaria since no available drug can clearly destroy the sporozoites, which remain in the bloodstream in a short time before entering the liver. The most popular chemoprophylaxis are mefloquine and doxycycline, suppressive agents that kill schizonts in the bloodstream; however, they do not act on the parasite in the liver.[2]

Mefloquine is well-known as a chemoprophylaxis agent for more than twenty years. It is claimed as an effective schizonside of all malaria species, including the newer Plasmodium knowlesi, which prevents the chloroquine-resistant Plasmodium falciparum (CRPF). Despite its benefit, this drug has produced a long debate among stakeholders worldwide due to its adverse effects, which are mainly psychosis, suicidal behaviour, or hallucination.[3,4] This issue rapidly raised among military personnel who take mefloquine for a longer time as compared to usual travelers or visitors.[5]

We reported a case of *Plasmodium ovale* infection in a young Indonesian soldier who had taken mefloquine prophylaxis for one year due to his service in Congo, Africa. Since *P. ovale* infection is mild and among the most infrequently reported cases of malaria worldwide, therefore, the efficacy of mefloquine to prevent this infection has brought out a big question mark.[6] While numerous papers have reviewed about its adverse events, there are limited data available about mefloquine efficacy to prevent *P. ovale*. Several potential mechanisms of this prophylaxis failure are also interesting to be discussed further.

CASE ILUSTRATION

A 22-year-old Indonesia soldier came with a complaint of high fever and chills, which had lasted for four days. He had just come back from United Nations service in Congo, Africa, three weeks before. Fever was followed by nausea and vomiting. The patient and his colleagues in Indonesia's military personnel attributable to service in Congo have already taken mefloquine dosage 250 mg weekly for one year due to this assignment. They had routinely taken the medication on a regular basis, as declared in the prerequisite checklist card prior to their duty. No symptom of insomnia, depression, anxiety, or significant neurological events was found. No history of prior malaria was recorded in this patient.

There was no skin rash nor sign of bleeding. His liver was mildly enlarged, but no splenomegaly was palpated. His laboratory examination revealed the following: anemia 10.8 g/dL with normocytic normochromic morphology, mild leucopenia 4,600/µL, and thrombo-cytopenia 105,000/µL. There was a little increase of AST (56 U/L) and ALT (42 U/L), but no abnormality was found in ureum, creatinine, blood glucose level, and electrolytes levels. Other possible infections were excluded by normal urinalysis and chest X-ray, negative Tubex® test, leptospira IgM, and normal procalcitonin levels. Dengue IgM and IgG antibody were also checked following the sixth day of fever, and negative result was found. Blood cultures did not yield any result. Rapid diagnostic test was negative for both HRP2 (for P. falciparum) and pLDH (for P. vivax); however, we determined positive P. ovale infection under the light microscopy with Giemsa's staining (**Figure 1**). He had 35/250 paracites under small microscopic view.

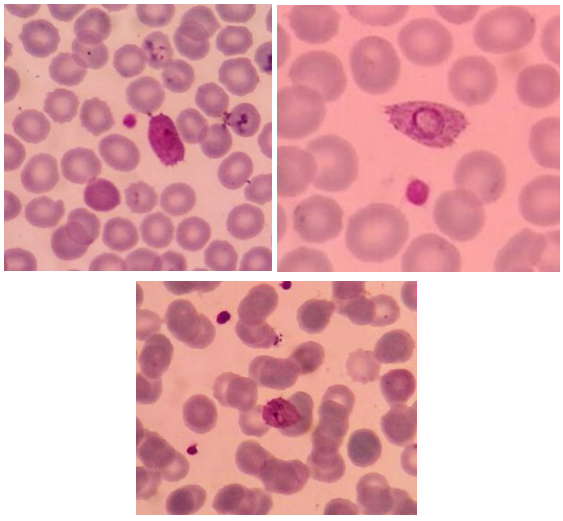

Figure 1. Giemsa-stained thin blood films of the patient (viewed under 1000x magnification).
(a) Gametocyte; (b) Rings in fimbriated red blood cells; (c) Trophozoites have sturdy cytoplasm, large chromatin dot, showing Schüffner dots.

The patient was then treated with dihydroartemisinin for 3 days and primaquine for 14 days. The parasites were shown negative since the third day following treatments.

DISCUSSION

Although most malaria cases are dominated by *P. falciparum* and *P. vivax*, for certain reasons– in this case, mandatory duty for military personnel – chemoprophylaxis for other species including *P. ovale* is warranted.[5] French military personnel who took doxycycline chemoprophylaxis experienced an increase of *P. ovale* infection after returning from Ivory Coast, West Africa, between 2002 and 2007; within the same period, they experienced a lower incidence rate of *P. falciparum* infection.[7] This phenomenon may imply the lower effectiveness of doxycycline on *P. ovale* than on *P. falciparum*; despite other possibilities of changes in local transmission.

The prevalence of *P. ovale* infection in West and Central Africa is around 10%, which is significantly higher compared to other regions in of the world (ranged 2-5%).[6,8] With the incubation period of 10-17 days, this type of malaria usually causes mild disease with low parasetemia. Only a few of publications reported severe and complicated cases due to *P. ovale*.[9,10]

This case illustration raised several questions about *P. ovale* infection after one year mefloquine prophylaxis. First, the influence of dormant stage of *P. ovale* during exposure period in Africa that might relapse later when coming/returning back to Indonesia. Second, the presumption of quinoline resistance in *P. ovale* could not be excluded yet. And the last, it is rationale to question the efficacy of mefloquine in minor species (ovale and malaria) that is limited in publication or clinical trial.

Dormant Stage of *P. ovale* and Clinical Implications

Evidences showed that *P. ovale* and *P. vivax* are associated with the relapse of malaria cases, which is caused from quiescent intracellular hepatic parasite stadium called hypozoites. Relapse cases are different with recrudescence, that originates from the circulation of parasite blood stages which do not cause fever before a certain level of parasitemia is reached. Recrudescence typically occurs due to P. falciparum, *P. knowlesi*, and *P. malariae* infections. True relapses, on the other hand, occur most frequently in *P. vivax*, less frequently in *P. ovale* and *P. malariae*, but have never been documented so far in *P. falciparum* and *P. knowlesi*.[11,12]

According to Richter, et al[12], only 5 of 240 patients of *P. ovale* infections, in which primaquine was not given, suffered a relapse. In contrast, several relapses despite primaquine prophylaxis have been described. This could be explained by insufficient resorption of primaquine, or the presence of quiescent extrahepatic plasmodial development stages that is insensitive to primaquine.

Quinoline-Resistant *P. ovale*

There are limited reports on drug resistance in *P. ovale*. However, the high burden of quinoline-resistance *P. falciparum* also raises arguments that similar phenomena might possibly happen in minor Plasmodium. These arguments are supported by several severe and complicated malaria case reports such as acute respiratory distress syndrome, end-stage renal failure, or splenic rupture or infarction following *P. ovale* infection.[13,14] Lau, et al[15] has reported a fatal *P. ovale* case in a 59-year-old male in Victoria Island, Nigeria, after 6 months of mefloquine. However, the pathophysiology and risk factors for its severe infection have not yet fully established.

Using in vitro and in vivo studies, Siswantoro H, et al[16] described the potential of quinoline resistance (chloroquine and mefloquine) in *P. ovale* and *P. malariae* in malaria subjects in Papua, Indonesia. However, subjects infected by *P. ovale* responded rapidly to treatments; all subjects were afebrile within 24 hours and aparasitemic within 48 hours.[16]

Efficacy of Mefloquine in *P. ovale*

Mefloquine was first developed in 1970s by US military's Walter Reed Army Institute of Research (WRAIR) in response to the increasing number of chloroquine-resistant *P. falciparum* in Southeast Asia. It was licensed and introduced to civilian market, targeted mainly on travelers,

in late 1980s and soon became widely used as chemoprophylaxis.[17] This drug is still used by several military forces for many years, such as US Soldier until 2009, and to date in Canada, Australia, UK, as well as Indonesia.[4,5,18]

Mefloquine is a fluorinated 4-quinoline methanol compound, and its parasiticidal action is similar to that of quinine.[19] In addition to antimalarial prophylaxis, this drug is also widely used to treat uncomplicated multi-drug-resistance falciparum malaria in combination with artesunate. As an anti-falciparum agent, a single dose alone could be practically used, but this leads more rapidly to resistance, thus it is no longer recommended.[1,17]

No literature has reported the real number of efficacy of mefloquine as malaria prevention. However, Lee, et al[20] reported a severe *P. ovale* infection in a 31-year-old female after 10 months of mefloquine prophylaxis in Ghana (parasitemia 0.1%). Surprisingly, the subject fully recovered with chloroquine and primaquine treatment (the same types of drugs).[20]

CONCLUSION

A case of *P. ovale* infection persisting after one year of mefloquine prophylaxis was reported. Several reasons may explain this phenomenon, however, it is still required to refining the benefit and risk of mefloquine as the chemoprophylaxis in the military.

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